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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/582,842	07/05/2000	KAZUYUKI SUGIYAMA	Q60017	2682

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EXAMINER	
DO, PENSEE T	
ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 07/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/582,842	SUGIYAMA ET AL.	
	Examiner	Art Unit	
	Pensee T. Do	1641	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 09 May 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☒ Applicant's reply has overcome the following rejection(s): *112, 2nd paragraph*.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☐ The a)☐ affidavit, b)☐ exhibit, or c)☐ request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1-3,6-12 and 24-30*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

DETAILED ACTION

Amendment Entry & Claim Status

The after-final amendment filed on May 9, 2003 has been acknowledged and entered.

Claims 1-3, 6-12, 24-30 are pending.

Withdrawn Rejection(s)

Rejection under 35 USC 112, 2nd paragraph in the previous office action is withdrawn herein.

Response to Arguments

The argument filed on May 9, 2003 has been fully considered but not found persuasive.

Regarding formal matters: please disregard the objection to the abstract and the specification in the previous office action.

Regarding the 103(a) rejection by Haughland et al. in view of Giese, Applicants submit that Giese does not teach or suggest that the crosslinked avidin disclosed therein is more stable, nor does Giese teaches that the crosslinked avidin has a higher biotin affinity than non-crosslinked avidin. Applicants further submit that the crosslinking treatment disclosed by Giese is a method which may be optionally carried out for stabilizing the multiple layer as a whole, but not a method for stabilizing only the avidin by forming an intramolecular crosslinkage. Furthermore, Applicants discussed that in the crosslinking treatment disclosed by Giese, not only an intramolecular crosslinkage of the protein (such as avidin), but also various crosslinkages (for example an

intermolecular crosslinkage between proteins, between the extenders (such as biotin), or between the protein and the extender, or an intramolecular crosslinkage of the extender) are formed.

Regarding the 103(a) rejection by Haughland in view of Giese and further in view of Tatsumi, Applicants argue that since the combination of Haughland and Giese does not make obvious the biotin-avidin complex of the present application and Tatsumi does not cure the defects of Giese discussed above, one of ordinary skill in the art would not have been motivated to combine Haughland, Giese and Tatsumi to arrive at the present invention.

As stated by Applicants "crosslinking treatment disclosed by Giese is to stabilize the multiple layer as a whole, but not a method of stabilizing only the avidin by forming an intramolecular crosslinkage and the multiple layer comprises of successive or repetitive attachment of proteins (such as avidin)", although that statement may be true, it is still a method of crosslinking avidin and that whether as a whole or not, the avidin which is part of the multiple layer is stabilized. Furthermore, the claims of the present invention are not a method of stabilizing avidin only. Therefore, Giese has disclosed the missing required components with respect to Haughland for one of ordinary skill in the art to find it obvious to arrive at the present invention. The present invention also fails to exclude any other crosslinkage other than avidin since they contain an opening claim language.

Regarding the 103(a) by Haughland, Giese and Tatsumi, since Giese satisfies the requirement of the present claims in combination with Haughland, one of ordinary

skills in the art would be motivated to combine Haughland, Giese and Tatsumi to arrive at the present invention.

Maintained Rejection(s)

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 6, 7-9, 12, 24, 27-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haughland et al. (US 5,443,986) further in view of Giese (US 4,478,914).

Haughland teaches a biotin-avidin-biotin complex comprising two biotin-introduced products which are the same or different (see table 12 in col. 22); and a avidin sandwiched therebetween (see col. 22, table 12) wherein at least one of the two biotin-introduced products is labeled and the other one is a biotin-introduced binding component (see col. 22). Haughland also teaches an enzyme-mediated technique such as enzyme-linked immunosorbent assay (ELISA) to detect analytes (see col. 22, lines 4-51). The method of the assay comprises combining the biotin-introduced enzyme, the sample containing analyte, and the biotin-binding component, an avidin to connect the two biotins together. The signal of the enzyme is detected. The binding component is a DNA (see col. 22, table 12). The biotin-introduced labeling substance is a biotin-

introduced enzyme (see col. 22, table 12). Kits containing reagents for carrying out the methods are also disclosed in Haughland (see col. 40, example 19).

However, Haughland fails to teach a cross-linked avidin.

Giese teaches a process comprises of applying alternate successive layers of a first *or* second materials to a surface to be modified. The first material comprises a ligand binding proteinaceous material and the second material comprises a reactive ligand extender material, wherein the proteinaceous first material is selected from the group consisting of lectins, protein A, avidin derivatives including a crosslinked avidin, streptavidin, antibodies and combinations thereof, the second material is selected from biotin, biotin derivatives, biotin analogs, Fc fragments, hapten and combinations thereof. Avidin is a protein found in egg whites. (see col. 1, lines 15-20; line 50-col. 4, line 62).

It would have been obvious to one of ordinary skill in the art to use the crosslinked avidin of Giese in the method of Haughland since Giese's end product would have layers of biotin-avidin-biotin on a solid support. Furthermore, the crosslinked avidin is more stable and has high biotin affinity than the non-crosslinked avidin and thus the complex of biotin-crosslinked avidin-biotin would be more stable. An increase in affinity and stability between the avidin and the biotin would be an advantage in reduced product storage. Assays and kits comprising increased affinity avidin, because of the additional stability, have a longer shelf and less fastidious in shipping and storage requirements. The enhanced stability of these assays and kits would reduce the cost to the consumer. Regarding claim 8, since Giese teaches that the second material is a biotin or biotin derivatives, Fc fragments, and combinations thereof, it would have been

obvious to one of ordinary skills in the art to combine biotin and Fc fragments to detect antigen since antibody fragment such as Fc fragment efficiently binds to the antigen more specifically with high affinity.

Claims 10, 11, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haughland et al. (US 5,443,986) and Giese further in view of Tatsumi (US 5,843,746).

Haughland et al. and Giese have been discussed above.

However, Haughland and Giese fail to teach a biotin-introduced fused-protein of an enzyme such as a biotin-introduced luciferase.

Tatsumi teaches a fusion protein (biotinated firely luciferase) which can be applied to a variety of bioluminescent analysis methods. For example, the biotinated firely luciferase can be bound through the biotin thereof to avidin or streptavidin to form a luciferase complex and a luminescent analysis method using such a firely luciferase complex can be applied to a detection system using biotin-avidin in techniques such as enzyme immunoassays, DNA probe method, immunostaining, receptor measurement, in situ hybridization, etc. (see col. 3, lines 33-41; col. 4, lines 25-35). Tatsumi also teaches using goat anti-mouse IgG Fc fragment-specific polyclonal antibody in the method of detecting for the enzyme activity. (see col. 7, lines 40-55).

It would have been obvious to one of ordinary skill in the art to use the fused protein of Tatsumi in the combined method of Haughland and Giese for detecting the activity of luciferase since Haughland teaches an enzyme immunoassay method of using binding agent-biotin-avidin-biotin-enzyme and the enzyme luciferase of Tatsumi

can be biotinylated. Since the biotinated firely luciferase of Tatsumi yields a much higher percentage of activity upon binding to streptavidin compared to that of a chemically modified biotinated firely luciferase, e.g. 93% to 62% respectively. Furthermore, the biotinated firely luciferase of Tatsumi attains 10 times sensitivity as high as the conventional chemically modified biotinated firely luciferase. With respect to the fragment Fab', since it depends on the analyte being detected, one of ordinary skill in the art would find it obvious to use fragment Fab's in the detection of antigen since fragment Fab' provides specificity

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pensee T. Do whose telephone number is 703-308-4398. The examiner can normally be reached on Monday-Friday, 7:00-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 703-305-3399. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-746-5291 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Christopher L. Chin

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP 1800/1641

Pensee T. Do
Patent Examiner
June 27, 2003